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ART UNIT

PAPER NUMBER

1805

DATE MAILED:

09/03/96

Please find below a communication from the EXAMINER in charge of this application.

Commissioner of Patents

Office Action Summary

Application No.

08/475,470

Applicant(s)

Richard J. Samulski, et al.

Examiner

Amy J. Nelson

Group Art Unit

1805



☒ Responsive to communication(s) filed on Jun 7, 1995

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-35 and 39 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-35 and 39 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been
☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

☒ Notice of Deposit Requirement

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

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DETAILED ACTION

Election/Restriction

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:
 - I. Claims 1-35, 39, drawn to a recombinant adeno-associated virus vector, classified in class 435, subclass 320.1.
 - II. Claims 36-38, 40-45 drawn to a method of using a recombinant adeno-associated virus vector for treating various blood disorders, classified in class 424 , subclass 93.1.
2. The inventions are distinct, each from the other because of the following reasons: Groups I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the treatment of blood disorders can be accomplished with a product other than the recombinant adeono-associated virus vector such as treatment with supplemental iron.
3. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

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4. During a telephone conversation with Arnold Silverman on July 16, 1996 a provisional election was made without traverse to prosecute the invention of Group I, claims 1-35, 39. Affirmation of this election must be made by applicant in responding to this Office action. Claims 36-38, 40-45 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.
5. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(h).

Oath/Declaration

6. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

Applicant (third inventor only) has not given a post office address anywhere in the application papers as required by 37 CFR 1.33(a). A statement over applicant's signature providing a complete post office address is required.

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Specification

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C 112, first paragraph, as failing to provide an enabling disclosure.

It is apparent that the recombinant adeno-associated virus vectors, rAAV/HS2/gammaglobin/neo, pJM24/vHS432γ, pAAV/FACC/Neo, are required to practice the claimed invention. As a required element it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 U.S.C. 112, first paragraph, may be satisfied by a deposit of the vectors, see 37 C.F.R. 1.802. Without a publicly available deposit of the above, one of ordinary skill in the art could not be assured of the ability to make the vectors in the same manner as claimed. Given the lack of guidance in the specification and inability of those in the art to reproduce specific vectors, it would require undue experimentation for one skilled in the art to make those vectors. If it is not so obtainable or available, the enablement requirements of 35 U.S.C. 112, first paragraph, may be satisfied by a deposit of the vectors. See 37 CFR 1.802.

Deposit of the vectors would satisfy the enablement requirements of 35 U.S.C. 112, first paragraph.

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If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 CFR 1.808.

If a deposit is not made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the following criteria have been met:

(a) during the pendency of this application, access to the deposits will be afforded to one determined by the commissioner to be entitled thereto;

(b) all restrictions imposed by the depositor on the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application;

(c) the deposits will be maintained in the public depository for a period of at least thirty years from the date of the deposit or for the enforceable life of the patent or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

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(d) a viability statement in accordance with the provisions of 37 CFR 1.807; and

(e) the deposits will be replaced if they should become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification.

In addition, the identifying information set forth in 37 CFR 1.809(d) should be added to the specification. See 37 CFR 1.803-37 CFR 1.809 for additional explanation of these requirements.

Claim Rejections - 35 USC § 112

8. Claims 18, 32, 35, 38 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

9. Claims 1-35, 39 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a full length protein, does not reasonably provide enablement for a biologically active fragment thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Applicant claims a recombinant adeno-associated virus vector comprising a eukaryotic nucleic acid sequence encoding a therapeutic protein or a biologically active fragment thereof. The specification teaches how to make said vector comprising a gamma globin, β -galactosidase, or FACC gene. The specification does not teach how to make said vector comprising biologically active fragments of genes encoding therapeutic proteins. **Ex parte Forman**, 230 USPQ (BPAI

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1986) lists eight considerations for determining whether or not undue experimentation would be necessary to practice an invention. These factors are: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples of the invention, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. The state of the art for determination of biological activity and for construction of viral vectors is highly unpredictable and hence significant guidance is required to practice the are without undue experimentation. The instant invention is not enabled given the lack of guidance in the specification and the unpredictability in the art, relating to the large number of potential gene fragments that would have to be tested to determine those that are biologically active, and the construction of adeno-associated viral vectors containing said fragments. When the Forman factors are weighed it is concluded that undue experimentation would be required to practice the invention throughout the full scope of the claims, and therefore the invention is not enabled.

10. Claim rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

At claim 1, line 6, the phrase "biologically active fragment" is unclear because the size of the fragment is unknown, as is the type and range of biological activity. Appropriate correction is required.

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At claim 7, lines 1-2, the phrase "eukaryotic cis-acting regulatory sequence" lacks proper antecedent basis. Appropriate correction is required.

At claim 9, line 2 the phrase "is responsible for encoding" is indefinite for it is not clear whether or not it encodes the globin protein. It is recommended that it be replaced with -- that encodes--.

At claim 11, line 4, the term "hypersensitive site IV" is repeated twice. One occurrence should be deleted.

At claim 12, line 3, the phrase "biologically active fragment" is unclear because the size of the fragment is unknown, as is the type and range of biological activity. Appropriate correction is required.

At claim 14, line 4, the term "hypersensitive site IV" is repeated twice. One occurrence should be deleted.

At claim 15, line 2, the phrase "biologically active fragment" is unclear because the size of the fragment is unknown, as is the type and range of biological activity. Appropriate correction is required.

At claim 17, line 3, the phrase "biologically active fragment" is unclear because the size of the fragment is unknown, as is the type and range of biological activity. Appropriate correction is required.

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At claim 27, line 5, the phrase "biologically active fragment" is unclear because the size of the fragment is unknown, as is the type and range of biological activity. Appropriate correction is required.

At claim 29, line 4, the term "hypersensitive site IV" is repeated twice. One occurrence should be deleted.

At claim 30, line 2-3, the term "hypersensitive site IV" is repeated twice. One occurrence should be deleted.

At claim 31, line 2, the phrase "biologically active fragment" is unclear because the size of the fragment is unknown, as is the type and range of biological activity. Appropriate correction is required.

Effective Filing Date

Applicant claims priority to 08/344,816, which is a CIP of 07/923,418, which is a CIP of 07/893,513, filed on 6/3/92. No disclosure of the embodiment of the invention pertaining to claims 33-35 is made in the specification of any of the parent applications. Hence, for those claims applicant is only entitled to an effective filing date of the instant application, that is 6/7/95.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

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A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 1-26 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Walsh *et al.* (Clin. Res. 39 (2): 325A, 1991).

Walsh discloses a recombinant adeno-associated virus comprising a gamma globin gene linked to the locus control region (LCR), more specifically hypersensitive site (HS) II, that could be stably transduced into the immune erythroleukemia (K562) cells, resulting in high levels of expression of the globin gene. Hence, all of the claim limitations of claims 1-26 are disclosed by Walsh.

13. Claims 33-35 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Walsh *et al.* (Blood 82 (10 suppl. 1): 347a, 1993).

Walsh discloses a recombinant adeno-associated virus that comprises a Fanconi anemia C complementing (FACC) gene linked to a Rous sarcoma virus (RSS) promoter that allows correction of Fanconi anemia in transduced CD34+ cells. All of the claim limitations of claims 33-35 are disclosed by Walsh.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

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such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

15. Claims 27-32, 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Walsh *et al.* (Clin. Res. 39 (2): 325A, 1991).

Applicant claims a recombinant adeno-associated virus as disclosed in claims 1-26 and described *supra*, that allows gene expression in hematopoietic cells. Although it is not clear what is intended by claim 30, it is believed that applicant claims a recombinant vector comprising all of HS IV, HS III and HS II. Applicant also claims a recombinant vector containing the gene for Factor IX protein.

The teachings of Walsh are described *supra*. Walsh does not teach the inclusion of all components of the locus control region, i.e. all of the hypersensitive sites, in a single vector, nor does he teach the inclusion of a gene for Factor IX protein in a recombinant adeno-associated viral vector. Furthermore, Walsh does not teach transduction of human hematopoietic cells. It would have been obvious to one of ordinary skill in the art at the time of applicant's invention to use hematopoietic stem cells instead of erythroid progenitor cells since both are immune cells and are deemed to be functional equivalents and it is obvious to substitute one functional equivalent for another. It also would have been obvious to use the entire LCR region rather than just HSII to achieve higher expression of the globin gene, and to substitute the Factor IX gene for the globin gene to overcome deficiencies in Factor IX associated with Hemophilia B.

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16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy J. Nelson whose telephone number is (703) 306-3218. The examiner can normally be reached on Monday-Friday from 7:30 AM -4:00 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mindy Fleisher, can be reached at (703) 308-0407. The fax phone number for this Group is (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Amy J. Nelson

August 29, 1996



**NANCY DEGEN
PATENT EXAMINER
GROUP 1800**